Beat-to-Beat, Reading-to-Reading, and Day-to-Day Blood Pressure Variability in Relation to Organ Damage in Untreated Chinese

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Abstract—Whether target organ damage is associated with blood pressure (BP) variability independent of level remains debated. We assessed these associations from 10-minute beat-to-beat, 24-hour ambulatory, and 7-day home BP recordings in 256 untreated subjects referred to a hypertension clinic. BP variability indices were variability independent of the mean, maximum–minimum difference, and average real variability. Effect sizes (standardized β) were computed using multivariable regression models. In beat-to-beat recordings, left ventricular mass index (n=128) was not (P≥0.18) associated with systolic BP but increased with all 3 systolic variability indices (+2.97–3.53 g/m^2; P<0.04); the urinary albumin-to-creatinine ratio increased (P≤0.03) with systolic BP (+1.14–1.17 mg/mmol) and maximum–minimum difference (+1.18 mg/mmol); and pulse wave velocity increased with systolic BP (+0.69 m/s; P<0.001). In 24-hour recordings, all 3 indices of organ damage increased (P<0.03) with systolic BP, whereas the associations with BP variability were nonsignificant (P≥0.15) except for increases in pulse wave velocity (P<0.05) with variability independent of the mean (+0.16 m/s) and maximum–minimum difference (+0.17 m/s). In home recordings, the urinary albumin-to-creatinine ratio (+1.27–1.30 mg/mmol) and pulse wave velocity (+0.36–0.40 m/s) increased (P<0.05) with systolic BP, whereas all associations of target organ damage with the variability indices were nonsignificant (P≥0.07). In conclusion, while accounting for BP level, associations of target organ damage with BP variability were readily detectable in beat-to-beat recordings, least noticeable in home recordings, with 24-hour ambulatory monitoring being informative only for pulse wave velocity. **(*Hypertension*. 2014;63:790-796.)** ● **Online Data Supplement**

Key Words: blood pressure monitoring, ambulatory ■ blood pressure monitoring, home ■ clinical laboratory science

The prognostic significance of blood pressure (BP) variability remains controversial. Some studies reported association of end-organ damage,[1–4] cardiovascular events,[5–7] or mortality[8] with BP variability, whereas others failed to do so or found variability to be inferior to level of systolic BP.[9–11] Whether naturally occurring BP variability predicts risk over and beyond BP level therefore remains debated. Part of the contradiction in the current literature[1–11] might find its origin in the technique used to measure BP, the interval over which BP variability is assessed, and the statistical indices applied to capture BP variability from recordings.[12] Expert opinion converges on the concept that beat-to-beat recordings are optimal to capture short-term BP variability, whereas intermittent ambulatory BP monitoring is less precise.[13] To our knowledge, no previous study assessed target organ damage in relation to beat-to-beat, reading-to-reading, and day-to-day BP variability. In addition, experts proposed avoiding measures of variability that are dependent on the BP level, such as the SD.[14,15]

To address the above issues, we ran multivariable-adjusted linear regression analyses to correlate left ventricular mass index (LVMI), the urinary albumin-to-creatinine ratio, and aortic pulse wave velocity (PWV) as continuous measures of target organ damage with BP level and variability in untreated Chinese patients referred to an outpatient clinic. We measured BP by 10-minute beat-to-beat recordings, 24-hour ambulatory registration, and home readings self-measured for 7 days. From these data sources, we quantified variability using recently proposed novel indices.[14,15]

Methods

Study Population

As described previously,[16] we recruited consecutive untreated patients referred for ambulatory BP monitoring to the Hypertension Outpatient Clinic of Ruijin Hospital, Shanghai, China. We adhere to the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Ruijin Hospital, Shanghai

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Jiaotong University School of Medicine. All patients gave informed written consent. Of those referred between February 2011 and December 2011, 259 were eligible for inclusion in the present analysis because they all had beat-to-beat, 24-hour ambulatory, and home BP measurements. The primary reason for referral was diagnosis of the BP status by 24-hour ambulatory BP monitoring in 236 (91.1%) never treated participants or confirmation of the indication for antihypertensive drug treatment in 23 (8.9%) patients after ≥2 weeks of discontinuation of antihypertensive agents. We excluded 3 patients from the analysis because the indices of organ damage were >3 SDs higher than the mean. Thus, the number of participants analyzed totaled 256.

BP Measurement

We programmed validated oscillometric SpaceLabs 90217 monitors (SpaceLabs, Redmond, Washington) to obtain ambulatory BP readings at 20-minute intervals from 06:00 to 22:00 and at 30-minute intervals from 22:00 to 06:00. Ambulatory hypertension was a 24-hour BP averaging 130 mm Hg systolic or 80 mm Hg diastolic or more. Office BP was measured with the Omron HEM-7051 monitor (Omron HealthCare, Kyoto, Japan). Office hypertension was a BP of ≥140 mm Hg systolic or 90 mm Hg diastolic. Using the BP monitor of the same type as in the office, participants obtained BP readings at home in triplicate in the morning before breakfast and again 3× in the evening before going to sleep during 7 consecutive days. Home hypertension was a BP of 135 mm Hg systolic or 85 mm Hg diastolic or more. Within 7 days after 24-hour BP monitoring, we recorded the beat-to-beat finger BP for 10 minutes with the Finometer device (Finapres Medical System, Amsterdam, The Netherlands). For further details of the BP measurement, see Expanded Methods in the online-only Data Supplement.

Assessment of Organ Damage

As described in detail elsewhere,[16] LVMI by echocardiography (n=128), the urinary albumin-to-creatinine ratio (n=256), and aortic PWV (n=255) were determined as measures of organ damage. For the details of the organ damage assessment and other measurements, including body mass index, serum cholesterol, plasma glucose, and questionnaire survey on smoking and drinking habits, see Expanded Methods in the online-only Data Supplement.

Statistical Analysis

For database management and statistical analysis, we used the Statistical Analysis System software, version 9.3 (SAS Institute, Cary, NC). We limited our main analyses to systolic BP because systolic BP is the main driver of risk[17] and because we recently demonstrated in the same patient cohort that systolic BP was the main determinant of target organ damage irrespective of age.[16] Henceforth, in our article unless otherwise specified, BP refers to systolic BP. We assessed BP variability from the variability independent of the mean (VIM),[15] the difference between maximum and minimum BP (MMD), and average real variability (ARV).[10,14] For the details of the computation of these variability indices, see Expanded Methods in the online-only Data Supplement.

To study the association between organ damage and BP level and variability, we first searched for covariables associated with BP variability in stepwise regression analysis with P values for explanatory variables to enter and stay in models set at 0.15. Next, we used multiple regression analysis to study the association of interest while adjusting for sex, age, body mass index, heart rate, fasting plasma glucose, total cholesterol, and smoking and drinking. Fully adjusted models included both BP level and an index of BP variability. We computed the variance inflation factor to assess to what extent parameter estimates for BP level and variability were affected by collinearity in fully adjusted regression models. Significance was an α-level of ≤ 0.05.

Results

Characteristics of the Participants

The 256 participants included 129 women (50.4%) and 17 (6.6%) patients with diabetes mellitus. Among women, the

Table 1. Characteristics of Participants by Blood Pressure Measurement Type and Median of Variability Independent of the Mean

	Finger Blood Pressure		24-H Blood Pressure		Home Blood Pressure	
Characteristic	<6.8 U	≥6.8 U	<13.6 U	≥13.6 U	<4.7 U	≥4.7 U
No. of subjects (%)	128 (50.0)	128 (50.0)	129 (50.4)	127 (49.6)	126 (49.2)	130 (50.8)
Women	58 (45.3)	71 (55.5)	60 (46.5)	69 (54.3)	47 (37.3)	82 (63.1)*
Smokers	28 (21.9)	24 (18.9)	26 (20.2)	26 (20.5)	35 (27.8)	17 (13.1)†
Drinking alcohol	22 (17.2)	21 (16.4)	19 (14.7)	24 (18.9)	22 (17.5)	21 (16.2)
Diabetes mellitus	11 (8.6)	6 (4.7)	10 (7.8)	7 (5.5)	5 (4.0)	12 (9.2)
Mean characteristic (±SD)						
Age, y	51.2±10.7	50.9±10.0	49.5±10.4	52.6±10.0‡	48.5±10.7	53.5±9.2*
Body mass index, kg/m^2	24.5±2.5	24.5±3.1	24.7±2.5	24.3±3.0	24.7±2.9	24.3±2.7
Systolic blood pressure, mm Hg	137.3±13.1	136.1±12.3	125.9±12.3	126.5±11.2	128.9±10.7	128.0±12.0
Diastolic blood pressure, mm Hg	77.8±7.8	76.1±8.4	82.1±10.1	81.3±9.3	82.4±9.2	78.5±8.7*
Heart rate, bpm	69.7±8.6	68.9±8.7	71.7±7.4	72.6±7.6	71.4±7.5	69.9±7.7
Maximum–minimum difference, mm Hg	34.6±11.5	56.8±27.2*	53.3±8.6	72.0±11.8*	9.8±2.6	18.9±5.7*
Average real variability, mm Hg	2.3±0.8	2.8±1.0*	8.6±1.4	9.9±1.6*	3.8±1.3	6.5±2.1*
Plasma glucose, mmol/L	4.94±0.85	5.12±1.06	5.04±1.11	5.02±0.80	5.04±1.09	5.02±0.83
Serum total cholesterol, mmol/L	4.93±0.78	4.99±0.93	4.85±0.90	5.07±0.81‡	4.93±0.89	4.99±0.83
Left ventricular mass index, g/m^2	92.7±14.4	96.0±16.7	94.1±16.0	94.6±15.1	92.4±15.5	96.3±15.5
Aortic pulse wave velocity, m/s	7.8±1.5	7.6±1.2	7.5±1.3	7.9±1.4‡	7.7±1.4	7.7±1.3
Albumin-to-creatinine ratio, mg/mmol	0.60 (0.16–2.51)	0.68 (0.17–3.86)	0.66 (0.16–2.97)	0.62 (0.18–2.94)	0.61 (0.16–3.00)	0.67 (0.18–2.77)

Diabetes mellitus was a plasma glucose level of 7.0 mmol/L or higher or use of antidiabetic drugs. Left ventricular mass index was available in 128 patients. The central tendency and spread of the urinary albumin-to-creatinine ratio are geometric mean and 5th to 95th percentile interval. To convert cholesterol and glucose from mmol/L to mg/dL, multiply by 38.6 or 18.0, respectively.

Significance of the difference with values below the midpoint: *P<0.001; †P<0.01; and ‡P<0.05.

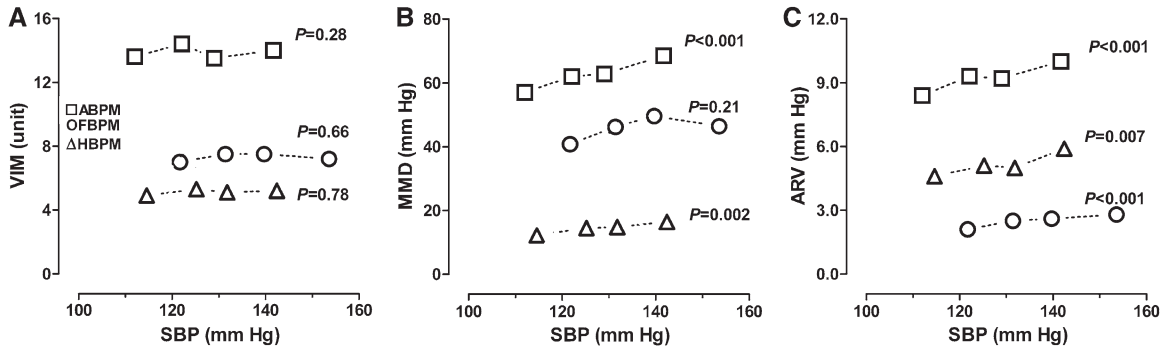

Figure. Variability independent of the mean (VIM, **A**), maximum–minimum difference (MMD, **B**), and average real variability (ARV, **C**) by quartiles of the distribution of the systolic blood pressure (SBP) on beat-to-beat (○, FBPM), 24-hour ambulatory (□, ABPM), or home (Δ, HBPM) measurement. *P* values are for linear trend across the quartiles of SBP.

prevalence of smoking and drinking was 0% and 3.9% and among men 40.9% and 29.9%, respectively. Age ranged from 29.1 to 71.3 years, averaging (±SD) 51.1±10.3 years (Figure S1 in the online-only Data Supplement). The prevalence of hypertension was 27.0%, 63.3%, and 39.8% on office, 24-hour, and home BP measurement, respectively. Expanded Results in the online-only Data Supplement and Table S1 provide information according to the cross-classification of participants based on office and out-of-the-office BP measurement and information on the quality assurance of the finger, 24-hour, and home BP measurement. Table 1 shows the characteristics of the participants by the median of the distribution of VIM derived from finger, 24-hour, and home BP recordings.

Correlates of the Variability Indices

In unadjusted analyses across quartiles of systolic BP level (Figure), VIM did not increase ($P \geq 0.28$), irrespective of the type of BP measurement. With the exception of MMD in beat-to-beat recordings ($P=0.21$), MMD and ARV increased ($P \leq 0.007$) across quartiles of systolic BP level.

We assessed the correlations between various indices of BP variability within and across measurement type (Table S2). As assessed by VIM, reading-to-reading pressure variability correlated with beat-to-beat ($r=0.15$; $P=0.015$) and day-to-day ($r=0.13$; $P=0.038$) variability, whereas the correlation between beat-to-beat and day-to-day VIM was low ($r=0.01$; $P=0.89$). We also performed stepwise regression analysis to identify correlates of systolic BP variability by type of BP measurement. The correlates differed for VIM, MMD, and ARV within and across measurement type (Table S3). The explained variance ranged from 2.3% to 26.2%.

Effect Sizes Associated With Level and Variability of Systolic BP

Beat-to-Beat Recordings

As shown in Table 2, LVMI was not associated with level of systolic BP in beat-to-beat recordings ($P \geq 0.18$), but independent of systolic BP and other covariables increased with VIM (+3.144 g/m^2; $P=0.005$), MMD (+3.528 g/m^2; $P=0.002$), and ARV (+2.968 g/m^2; $P=0.038$). The urinary albumin-to-creatinine ratio independently increased with the level of systolic BP (+1.139–1.169 mg/mmol; $P \leq 0.03$) and MMD (+1.183 mg/mmol; $P=0.003$). PWV only increased with the level of systolic BP (+0.689 m/s; $P<0.001$). In all models including both level and variability of beat-to-beat BP, the variance inflation factor did not exceed 1.24.

Table 2. Association of Organ Damage With Level and Variability of Systolic Blood Pressure Derived From Beat-to-Beat Recordings

Correlate (Approximate SD)	Model	Left Ventricular Mass Index, g/m^2	Albumin-to-Creatinine Ratio, mg/mmol	Pulse Wave Velocity, m/s
SBP (+13 mm Hg)	None	1.209 (–1.619 to 4.037)	1.169 (1.055 to 1.294)†	0.689 (0.562 to 0.816)*
	VIM	1.924 (–0.853 to 4.701)	1.169 (1.055 to 1.294)†	0.689 (0.562 to 0.816)*
	MMD	1.456 (–1.270 to 4.182)	1.139 (1.028 to 1.261)‡	0.689 (0.562 to 0.816)*
	ARV	0.533 (–2.321 to 3.387)	1.139 (1.028 to 1.261)‡	0.689 (0.536 to 0.842)*
VIM (+2 U)	None	2.882 (0.753 to 5.011)†	1.051 (0.965 to 1.146)	–0.074 (–0.199 to 0.051)
	SBP	3.144 (0.992 to 5.296)†	1.051 (0.969 to 1.141)	–0.074 (–0.180 to 0.032)
MMD (+24 mm Hg)	None	3.480 (1.269 to 5.691)†	1.183 (1.077 to 1.300)†	0.024 (–0.117 to 0.165)
	SBP	3.528 (1.317 to 5.739)†	1.183 (1.077 to 1.300)†	–0.048 (–0.189 to 0.093)
ARV (+1 mm Hg)	None	3.083 (0.386 to 5.780)‡	1.163 (1.031 to 1.311)‡	0.234 (0.056 to 0.412)‡
	SBP	2.968 (0.195 to 5.741)‡	1.113 (0.982 to 1.261)	–0.006 (–0.167 to 0.155)

Model indicates which systolic index was entered into the models in addition to the predictor variable per se. None indicates that no systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in target organ damage associated with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, and smoking and drinking. ARV indicates average real variability; MMD, the difference of maximum minus minimum systolic blood pressure; SBP, systolic blood pressure; and VIM, variability independent of the mean.

Significance of the estimates: *$P<0.001$; †$P<0.01$; and ‡$P<0.05$.

Table 3. Association of Organ Damage With Level and Variability of Systolic Blood Pressure Derived From 24-Hour Ambulatory Monitoring

Correlate (Approximate SD)	Model	Left Ventricular Mass Index, g/m^2	Albumin-to-Creatinine Ratio, mg/mmol	Pulse Wave Velocity, m/s
SBP (+12 mm Hg)	None	3.216 (0.605 to 5.827)‡	1.241 (1.103 to 1.397)*	0.420 (0.255 to 0.585)*
	VIM	3.204 (0.570 to 5.838)‡	1.241 (1.103 to 1.397)*	0.420 (0.255 to 0.585)*
	MMD	3.156 (0.357 to 5.955)‡	1.271 (1.130 to 1.430)*	0.360 (0.195 to 0.525)*
	ARV	3.792 (1.017 to 6.567)†	1.287 (1.143 to 1.448)*	0.444 (0.279 to 0.609)*
VIM (+3 U)	None	0.363 (–2.525 to 3.191)	0.939 (0.845 to 1.044)	0.165 (0.006 to 0.324)‡
	SBP	0.249 (–2.550 to 3.060)	0.933 (0.839 to 1.448)	0.156 (0.003 to 0.309)‡
MMD (+14 mm Hg)	None	1.330 (–1.551 to 4.211)	0.986 (0.883 to 1.101)	0.280 (0.115 to 0.445)*
	SBP	0.168 (–2.850 to 3.186)	0.932 (0.835 to 1.041)	0.168 (0.003 to 0.333)‡
ARV (+2 mm Hg)	None	–0.696 (–4.169 to 2.777)	1.021 (0.883 to 1.161)	0.126 (–0.078 to 0.330)
	SBP	–2.300 (–5.883 to 1.283)	0.898 (0.776 to 1.038)	–0.090 (–0.302 to 0.122)

Model indicates which systolic index was entered into the models in addition to the predictor variable per se. None indicates that no systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, and smoking and drinking. ARV indicates average real variability; MMD, the difference of maximum minus minimum systolic blood pressure; SBP, systolic blood pressure; and VIM, variability independent of the mean.

Significance of the estimates: *P<0.001; †P<0.01; and ‡P<0.05.

24-Hour Ambulatory Recordings

As shown in Table 3, independent of the 3 indices of BP variability, LVMI (+3.156–3.792 g/m^2; P≤0.029), the urinary albumin-to-creatinine ratio (+1.241–1.287 mg/mmol; P<0.001), and PWV (+0.360–0.444 m/s; P≤0.001) increased with higher level of systolic BP. The associations of organ damage with the indices of BP variability were all nonsignificant (P≥0.15) with the exception of an increase in PWV with VIM (+0.156 m/s; P=0.045) and MMD (+0.168 m/s; P=0.032). In all models including both level and variability of the 24-hour BP (Table 3), the variance inflation factor was not higher than 1.36. Sensitivity analyses based on daytime (Table S4) and nighttime (Table S5) BP were confirmatory.

Self-Measured Home Recordings

As shown in Table 4, independent of the 3 indices of BP variability, the urinary albumin-to-creatinine ratio (+1.274–1.302 mg/mmol; P<0.001) and PWV (+0.363–0.396 m/s; P≤0.001), but not LVMI (P≥0.43), increased with higher level of systolic BP. The associations of organ damage with all of the indices of BP variability on self-measurement were nonsignificant (P≥0.067). In all models including both level and variability of the home BP (Table 4), the variance inflation factor was not higher than 1.23. Sensitivity analyses based on the morning (Table S6) and evening (Table S7) home BP were confirmatory.

Additional Analyses

To allow comparison of our current results with the literature, we repeated our analyses using SD and coefficient of variation as indices of BP variability (Table S8). The associations of LVMI, the urinary albumin-to-creatinine ratio, and PWV with SD and coefficient of variation as estimated from beat-to-beat, 24-hour ambulatory, and home BP recordings confirmed the

Table 4. Association of Organ Damage With Level and Variability of Systolic Blood Pressure Derived From Home Self-Measurement

Correlate (Approximate SD)	Model	Left Ventricular Mass Index, g/m^2	Albumin-to-Creatinine Ratio, mg/mmol	Pulse Wave Velocity, m/s
SBP (+11 mm Hg)	None	1.089 (–1.606 to 3.784)	1.274 (1.143 to 1.419)*	0.363 (0.212 to 0.514)*
	VIM	1.111 (–1.606 to 3.828)	1.274 (1.143 to 1.419)*	0.363 (0.212 to 0.514)*
	MMD	1.056 (–1.704 to 3.816)	1.302 (1.169 to 1.451)*	0.363 (0.212 to 0.514)*
	ARV	1.089 (–1.628 to 3.806)	1.288 (1.156 to 1.435)*	0.396 (0.245 to 0.547)*
VIM (+2 U)	None	0.278 (–2.352 to 2.908)	0.947 (0.856 to 1.049)	–0.022 (–0.179 to 0.135)
	SBP	0.338 (–2.300 to 2.976)	0.940 (0.852 to 1.037)	–0.034 (–0.183 to 0.115)
MMD (+6 mm Hg)	None	0.396 (–2.391 to 3.183)	1.012 (0.910 to 1.125)	0.072 (–0.081 to 0.225)
	SBP	0.210 (–2.624 to 3.044)	0.942 (0.847 to 1.047)	–0.030 (–0.183 to 0.123)
ARV (+2 mm Hg)	None	0.962 (–1.743 to 3.667)	1.008 (0.914 to 1.112)	–0.046 (–0.195 to 0.103)
	SBP	0.962 (–1.747 to 3.671)	0.951 (0.862 to 1.049)	–0.134 (–0.279 to 0.011)

Model indicates which systolic index was entered into the models in addition to the predictor variable per se. None indicates that no systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking, and drinking. ARV indicates average real variability; MMD, the difference of maximum minus minimum systolic blood pressure; SBP, systolic blood pressure; and VIM, variability independent of the mean.

Significance of the estimates: *P<0.001.

findings reported in Tables 2, 3, and 4. In all of these analyses the variance inflation factor was <1.31. The analyses based on a balanced sample for all estimates (n=128) were also confirmatory (data not shown). Finally, analyses based on diastolic BP generated results similar to those based on systolic BP, although in general associations were weaker and significance levels lower (Table S9).

Discussion

To our knowledge, our article is the first that in the same participants addressed the association of organ damage with BP level and variability over differing periods, covering 10 minutes, daytime, nighttime, 24 hours, and 7 days. The key finding of our study was that the 3 indices of 10-minute BP variability were associated with LVMI independent of level and 10-minute MMD also with the urinary albumin-to-creatinine ratio. Furthermore, levels of the 24-hour and home BPs were associated with organ damage, whereas variability derived from such recordings was not associated with organ damage except for the relation of PWV with VIM and MMD derived from 24-hour ambulatory monitoring.

There is a physiological corollary possibly explaining our findings.[13] BP variability over very short (beat-to-beat) or short (within 24 hours) periods reflect the influence of central and reflex autonomic nervous modulation, the elastic properties of the central arteries, circulating hormones, blood viscosity, and psychological stress.[13] Although intermittent ambulatory BP monitoring is less precise in capturing short-term BP variations as compared with beat-to-beat recordings,[13] we previously demonstrated that BP variability by ambulatory monitoring contributed to the prediction of hard cardiovascular outcomes, albeit to a small amount.[10] Longer term BP variability, such as captured by self-measurement at home, does not entirely consist of spontaneous BP variations nor reflects the same cardiovascular control mechanisms as very short or short-term BP variability and is under the influence of behavioral between-day variability.[13]

Few other studies addressed the risk associated with BP variability as captured from beat-to-beat recordings. Parati et al[1] recorded 24-hour beat-to-beat BP intra-arterially and scored target organ damage in 108 untreated hospitalized patients. In analyses by quintiles, for nearly any level of the 24-hour BP, patients whose 24-hour BP variability was below average had a lower prevalence and severity of target organ damage than those with a higher than average BP variability.[1] Veerman et al[18] recorded BP level and variability during 20 minutes by means of the Finapres Model 5 in 33 untreated hypertensive patients. The urinary albumin-to-creatinine ratio correlated with diastolic (r=0.37; P=0.037) but not systolic BP variability. The associations of LVMI with systolic and diastolic BP variability were not significant.[18] The drawbacks of these previous studies were small sample size,[1,18] selection of hospitalized participants,[1] and categorical instead of continuous analyses.[1] In our study, all 3 studied indices of 10-minute beat-to-beat BP variability were associated with LVMI independent of level and 10-minute MMD also with the urinary albumin-to-creatinine ratio. However, the Finometer reliably captures BP variation or changes in BP in response to an intervention but might be less reliable in establishing a person's BP level.[19] This might explain in our study the absence of any association between LVMI and the systolic BP level as assessed by beat-to-beat recordings.

Turning to BP variability assessed from intermittent 24-hour ambulatory recordings, we previously demonstrated that ≥48 readings are required to compute BP variability without loss of prognostic information.[20] Tatasciore et al[2] reported in 180 untreated participants that LVMI was independently associated with awake systolic BP level and variability, whereas the rate of nocturnal (12 hours) microalbuminuria was related to awake systolic BP variability, but not level. A subsequent article by the same authors in an extended group of 309 patients concluded that higher BP variability with adjustment for left ventricular mass was associated with depressed indices of left ventricular function.[21] Although previous publications consistently demonstrated that nighttime BP level is a strong predictor of cardiovascular risk,[22] the association of nighttime BP variability with target organ damage remains to be elucidated. In our current study, all 3 measures of target organ were related to the nighttime systolic BP level but not variability, which is consistent with most,[23–25] although not all[26] previous studies.

In our current study, aortic PWV independently increased with level and VIM or MMD of systolic BP. Because of the cross-sectional nature of our study, we cannot distinguish cause from effect. We presume that with stiffer central arteries, BP must be more variable, systolic BP, and augmentation being buffered less in the large elastic arteries. Moreover, stiffening of the carotid arteries impairs baroreflexes. In 47 normotensive men, Monahan et al[27] observed that carotid arterial compliance was a strong determinant of baroreflex sensitivity, explaining 51% of the total variance. Similarly, 2 other studies involving younger[28] or older[29] healthy volunteers reported an inverse association between indexes of carotid stiffening and baroreflex sensitivity.

Finally turning to the self-measured BP at home, we noticed that none of the indices of target organ damage was associated with BP variability, as captured by VIM, MMD, or ARV. The Ohasama investigators recently reported that independent of morning systolic BP level, morning VIM and ARV predicted total and cardiovascular mortality (P≤0.044), whereas morning MMD did not predict any end point (P≥0.085).[30] However, the R^2 statistic, a measure for the incremental risk explained by adding BP variability to models already including level and covariables, ranged only from <0.01% to 0.88%.[30] The conclusion of the Ohasama investigators[30] that the indices of BP variability derived from home BP do not incrementally predict outcome over and beyond BP level is in keeping with our current findings based on the cross-sectional assessment of target organ damage. Home BP measurement provides less comprehensive information than ambulatory monitoring because substantially fewer readings are obtained within a 24-hour time window and because responses to an individual's physical and mental stressors are eliminated by obtaining the home BP measurements under standardized conditions in the morning and evening. The more restricted information provided by home BP measurement, in comparison with 24-hour ambulatory monitoring, both in terms of BP level and variability probably explains why in our current study systolic BP on home measurement was not

correlated with LVMI and why day-to-day BP variability was unrelated to the measures of target organ damage.

Our current study must be interpreted within the context of its limitations. First, the present study had a cross-sectional design. We assessed only intermediate signs of target organ damage and only 50% of our participants had LVMI measured. Our current observations can therefore not be extrapolated to the incidence of hard cardiovascular or renal end points. Second, our study participants were either normotensive individuals or untreated patients with mild hypertension, who were at relatively low cardiovascular risk. The low number of patients with left ventricular hypertrophy, microalbuminuria, or abnormally increased PWV made a meaningful logistic analyses with binary outcomes impossible. However, continuous traits, as used in the current article, provide fuller information than binary traits dichotomized by criteria that are often applied in clinical practice but always remain arbitrary to some extent. Notwithstanding this principle, future studies in high-risk patients with binary outcomes, such as left ventricular hypertrophy, microalbuminuria, or abnormally increased PWV, are warranted to confirm our current findings. Third, among our study participants, there was large discrepancy between the prevalence of hypertension as assessed by office and out-of-the-office BP measurement. Based on 24-hour ambulatory BP monitoring, normotension and white-coat, masked, and sustained hypertension had a prevalence of 32.0%, 4.7%, 41.0% and 22.3%, respectively. Based on the self-measured BP at home, these frequencies were 51.6%, 8.6%, 21.5%, and 18.4%, respectively. These findings probably reflect the indications for referral of our patients and highlight the need for a replication of our findings in a randomly selected population sample.

Perspectives

Beat-to-beat recordings, even as short as 10 minutes, outperform 24-hour ambulatory and home monitoring in the assessment of target organ damage in relation to BP variability, whereas the opposite is true for evaluating the contribution of BP level to organ damage. Current knowledge on the mechanisms of short-term BP variability is limited, and additional studies will be needed to improve our understanding of its potential determinants and prognostic implications. If confirmed in prospective studies with hard cardiovascular outcomes, our current findings potentially identified an easy way to assess short-term BP variability as a risk factor at least in individuals not on antihypertensive drug treatment.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study examined for the first time the independent associations of organ damage with level and variability of systolic blood pressure (BP) as captured from 10-minute beat-to-beat, 24-hour ambulatory, and 7-day home recordings.

What Is Relevant?

- Whether naturally occurring BP variability predicts risk over and beyond BP level remains debated.
- Beat-to-beat recordings might be optimal to capture short-term BP variability, whereas intermittent ambulatory BP monitoring is less precise.

Summary

While accounting for BP level, associations of target organ damage with BP variability were readily detectable in beat-to-beat BP recordings, least noticeable in home BP recordings, with 24-hour ambulatory monitoring being informative only for pulse wave velocity.

HYPERTENSION

(HYPE201302681DR3)

Supplemental Material

This Data Supplement has been provided by the authors to give readers additional information about their work.

Supplement to:
Wei F-F *et al*. Beat-to-Beat, Reading-to-Reading, and Day-to-Day Blood Pressure Variability in Relation to Organ Damage in Untreated Chinese (HYPE201302681DR3)

Expanded Methods

Blood Pressure Measurement

For all BP measurements at the brachial artery, we applied the recommendations of the European Society of Hypertension and adjusted cuff size to arm circumference.[1] We programmed validated oscillometric SpaceLabs 90217 monitors (SpaceLabs, Redmond, Washington) to obtain BP readings at 20-minute intervals from 06:00 to 22:00 and at 30-minute intervals from 22:00 to 06:00. All recordings covered more than 20 hours and included at least 70% of the programmed readings, without interval between readings longer than 2 hours, and were sparsely edited. The 24-h BP means were weighted for the time interval between consecutive readings.[2] Ambulatory hypertension was a 24-h BP averaging 130 mm Hg systolic or 80 mm Hg diastolic or more.[1] Office BP was measured with the Omron HEM-7051 monitor (Omron HealthCare, Kyoto, Japan).[3] After the participants had rested in the sitting position for at least 10 minutes, three consecutive readings were obtained. For analysis, the three readings were averaged. Office hypertension was a BP of at least 140 mm Hg systolic or 90 mm Hg diastolic. Participants obtained BP readings at home in triplicate in the morning before breakfast and again three times in the evening before going to sleep during 7 consecutive days. They did the self-measurements in the sitting position, using validated Omron HEM-7051 monitors.[3] The home BP was the average of all available readings. Home hypertension was a BP of 135 mm Hg systolic or 85 mm Hg diastolic or more.[1]

Within 7 days after 24-h BP monitoring, we recorded the beat-to-beat finger BP for 10 minutes after participants had rested for at least 10 minutes in the supine position. We used the validated[4,5] Finometer device (Finapres Medical System, Amsterdam, The Netherlands) that implements the volume-clamp method developed by Penáz.[6] The finger BP was calibrated using an upper arm cuff measurement and return to flow technology.[6] For analysis, we discarded the first minute of the recordings.

Assessment of Target Organ Damage

As described in detail elsewhere,[7] left ventricular mass index by echocardiography (n=128), the urinary albumin-to-creatinine ratio (n=256), and aortic pulse wave velocity (n=255) were determined as measures of organ damage. Briefly, echocardiograms were obtained according to the recommendations of the American Society of Echocardiography,[8] using a Phillips IE33 scanner (Phillips, Eindhoven, The Netherlands). A first-morning urine sample was collected for the measurement of the urinary albumin (in milligram) and creatinine (in millimoles) concentrations. Aortic pulse wave velocity was measured by sequential electrocardiogram-gated recordings of the arterial pressure waveform at the carotid and femoral arteries using the SphygmoCor device (AtCor Medical, West Ryde, New South Wales, Australia).[7]

Other Measurements

Nurses administered a standardized questionnaire, to inquire about each participant's medical history, intake of medications, and smoking and drinking habits. They also measured body height and waist circumference to the nearest 0.5 cm. Body mass index was weight in kilograms divided by the height in meters squared. Venous blood samples, collected after overnight fasting, were analyzed by automated enzymatic methods for serum cholesterol and plasma glucose. Diabetes mellitus was a fasting plasma glucose level of 7.0 mmol/L[9] or higher or use of antidiabetic drugs.

Statistical Analysis

We assessed BP variability from the variability independent of the mean (VIM),[10] the difference between maximum and minimum BP (MMD), and average real variability (ARV).[11] VIM is calculated as the SD divided by the mean to the power *x* and multiplied by the population mean to the power *x*.[10] The values of *x* for the finger, 24-h and home BP were 1.03, 0.61, and 1.11, respectively. ARV is the average of the absolute differences between consecutive BP measurements.[11]

Expanded Results

We subdivided our study population into normotensive subjects and patients with white-coat, masked or sustained hypertension. Based on 24-ambulatory blood pressure measurement, normotension and white-coat, masked and sustained hypertension had a prevalence of 32.0%, 4.7%, 41.0% and 22.3%, respectively. Based on the self-measured blood pressure at home, these frequencies we 51.6%, 8.6%, 21.5% and 18.4%, respectively. Multivariable-adjusted models not including blood pressure on 24-h or home measurement, demonstrated that sustained hypertension was associated with increased albumin-to-creatinine ratio ($P \leq 0.01$) and pulse wave velocity ($P < 0.001$), but not left ventricular mass index ($P \geq 0.47$). However, introducing systolic blood pressure on 24-h or home measurement removed the significance of the aforementioned associations ($P \geq 0.10$).

The median number of cardiac cycles in beat-to-beat recordings was 685 (5th to 95th percentile interval, 502–771). The median number of BP readings averaged for analysis was 60 (5th to 95th percentile interval, 49–64; range 43–65) for the 24-h BP and 42 (5th to 95th percentile interval, 36–42; range, 24–42) for the home BP. There was no preference in the terminal digits in the home BP measurement ($P = 0.78$). The number of identical systolic and diastolic readings in the morning or evening was less than 4% on any of the 7 measurement days (Table S1).

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Table S1. Within-Patient Number Preference for Home Blood Pressure Readings

Day	Morning Blood Pressure Measurements						Evening Blood Pressure Measurements					
	Systolic			Diastolic			Systolic			Diastolic		
	N_a	N_b	%	N_a	N_b	%	N_a	N_b	%	N_a	N_b	%
1	187	1	1	187	2	1	252	2	1	252	4	2
2	254	1	0	254	1	0	254	0	0	254	2	1
3	254	0	0	254	4	2	254	0	0	254	3	1
4	251	2	1	251	3	1	253	1	0	253	4	2
5	253	2	1	253	6	2	249	2	1	249	6	2
6	250	0	0	250	0	0	249	0	0	249	4	2
7	253	2	1	253	3	1	222	1	0	222	8	4

Day indicates the order of the measurement days. N_a denotes the number of patients with home blood pressure measurement on a specified day. N_b is the number of patients with 3 identical readings.

Table S2. Correlations between Systolic Indices Within and Across Types of Blood Pressure Recordings

Correlate	Beat-to-Beat				24-H Monitoring				Home Self-Measurement			
	SBP	VIM	MMD	ARV	SBP	VIM	MMD	ARV	SBP	VIM	MMD	ARV
Beat-to-Beat												
SBP	1	0.005	0.100	0.298‡	0.497‡				0.505‡			
VIM		1	0.691‡	0.444‡		0.152*				0.008		
MMD			1	0.425‡			0.069				–0.017	
ARV				1				0.130*				0.004
24-h Monitoring												
SBP					1	0.004	0.295‡	0.339‡	0.702‡			
VIM						1	0.816‡	0.450‡		0.130*		
MMD							1	0.515‡			0.174†	
ARV								1				0.151*
Home Self-Measurement												
SBP									1	–0.008	0.230‡	0.185†
VIM										1	0.944‡	0.755‡
MMD											1	0.784‡
ARV												1

Abbreviations: SBP, systolic blood pressure; VIM, variability independent of the mean; MMD, the difference of maximum minus minimum systolic blood pressure; ARV, average real variability. Values are Pearson correlation coefficients.
Significance of the correlation coefficients: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S3. Determinants of the Indices of Systolic Variability by Type of Blood Pressure Measurement (starts)

Regression Parameters	Variability Independent of the Mean (unit)	Maximum–Minimum Difference (mm Hg)	Average Real Variability (mm Hg)
Beat-to-Beat Recordings			
R^2	0.023	0.046	0.183
Effect size			
Female sex	…	…	0.379 (0.163 to 0.595)‡
Age (+10 years)	…	–2.370 (–5.192 to 0.452)	–0.110 (–0.208 to –0.012)*
Systolic pressure (+13 mm Hg)	…	2.886 (–0.044 to 5.816)	0.273 (0.171 to 0.375)‡
Body mass index (+3 kg/m^2)	…	3.732 (0.657 to 6.807)*	0.147 (0.035 to 0.259)*
Plasma glucose (+1 mmol/L)	0.385 (0.073 to 0.697)*	…	…
Smoking (0,1)	…	…	–0.011 (–0.021 to –0.001)*
24-h Monitoring			
R^2	0.031	0.115	0.262
Effect size			
Age (+10 years)	0.400 (0.047 to 0.753)*	1.330 (–0.297 to 2.957)	0.530 (0.354 to 0.706)‡
Systolic pressure (+12 mm Hg)	…	4.200 (2.530 to 5.870)‡	0.564 (0.376 to 0.332)‡
Heart rate (+8 beat/minute)	…	…	0.144 (–0.044 to 0.311)
Total cholesterol (+1 mmol/L)	0.376 (–0.053 to 0.805)	2.190 (0.299 to 4.081)*	0.194 (–0.016 to 0.404)
Drinking (0,1)	…	…	0.369 (–0.101 to 0.839)
Smoking (0,1)	…	…	–0.537 (–1.04 to –0.033)*

Table S3. Determinants of the Indices of Systolic Variability by Type of Blood Pressure Measurement (continues)

Regression parameters	Variability Independent of the Mean (unit)	Maximum–Minimum Difference (mm Hg)	Average Real Variability (mm Hg)
Home Self-Measurement			
R^2	0.107	0.170	0.134
Effect size			
Female sex	1.195 (0.695 to 1.695)‡	3.252 (1.749 to 4.755)‡	1.136 (0.615 to 1.657)‡
Age (+10 years)	0.270 (0.015 to 0.525)*	0.740 (–0.005 to 1.485)	…
Systolic pressure (+11 mm Hg)	…	1.760 (1.049 to 2.471)‡	0.517 (0.258 to 0.776)‡
Drinking (0,1)	0.643 (–0.065 to 1.351)	1.882 (–0.160 to 3.924)	0.659 (–0.060 to 1.378)

Effect sizes (95% confidence interval) express the change in the systolic indices associated with 1-SD increase in the baseline variables. R^2 is the coefficient of multiple determination and indicates the percentage of variance explained by the whole model. The variables considered in the stepwise regression procedure included: sex, age, body mass index, systolic blood pressure, heart rate, smoking and drinking, serum total cholesterol, and fasting plasma glucose. Variables were allowed to enter and stay in the model with the *P*-value set at 0.15.
Significance of the effect sizes: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S4. Association of Organ Damage with Level and Variability of Daytime Ambulatory Systolic Blood Pressure

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
SBP (+13 mm Hg)	None	3.250 (0.575 to 5.925)*	1.215 (1.097 to 1.346)‡	0.455 (0.302 to 0.608)‡
	VIM	3.224 (0.523 to 5.925)*	1.215 (1.097 to 1.346)‡	0.455 (0.302 to 0.608)‡
	MMD	2.990 (0.187 to 5.793)*	1.215 (1.097 to 1.346)‡	0.403 (0.250 to 0.556)‡
	ARV	3.640 (0.786 to 6.494)*	1.231 (1.084 to 1.398)‡	0.481 (0.303 to 0.659)‡
VIM (+3 units)	None	1.005 (–2.064 to 4.074)	1.000 (0.884 to 1.131)	0.180 (–0.008 to 0.368)*
	SBP	0.849 (–2.173 to 3.871)	0.985 (0.871 to 1.114)	0.147 (–0.029 to 0.323)
MMD (+13 mm Hg)	None	1.807 (–0.945 to 4.559)	1.040 (0.939 to 1.151)	0.286 (0.133 to 0.439)‡
	SBP	0.988 (–1.840 to 3.816)	0.987 (0.891 to 1.093)	0.195 (0.042 to 0.348)*
ARV (+2 mm Hg)	None	0.010 (–2.871 to 2.891)	1.037 (0.925 to 1.162)	0.144 (–0.028 to 0.316)
	SBP	–1.242 (–4.225 to 1.741)	0.951 (0.842 to 1.075)	–0.052 (–0.228 to 0.124)

Abbreviations: SBP, systolic blood pressure; VIM, variability independent of the mean; MMD, the difference of maximum minus minimum systolic blood pressure; ARV, average real variability. Daytime blood pressure (6 AM – 10 PM) was obtained by 24-h ambulatory monitoring excluding the transition periods in the morning and evening when blood pressure rapidly changes. Model indicates which systolic index was entered into the models in addition to the predictor variable *per se*. None indicates that no other systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking and drinking. Significance of the estimates: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S5. Association of Organ Damage with Level and Variability of Nighttime Ambulatory Systolic Blood Pressure

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
SBP (+12 mm Hg)	None	2.712 (0.125 to 5.299)*	1.241 (1.130 to 1.363)‡	0.264 (0.099 to 0.429)‡
	VIM	2.748 (0.161 to 5.335)*	1.226 (1.116 to 1.347)‡	0.264 (0.099 to 0.429)‡
	MMD	3.000 (0.342 to 5.658)*	1.256 (1.143 to 1.380)‡	0.276 (0.111 to 0.441)‡
	ARV	3.012 (0.425 to 5.599)*	1.256 (1.143 to 1.380)‡	0.276 (0.111 to 0.441)‡
VIM (+4 units)	None	–1.252 (–4.427 to 1.923)	0.916 (0.814 to 1.030)	–0.112 (–0.292 to 0.068)
	SBP	–1.400 (–4.536 to 1.736)	0.923 (0.820 to 1.039)	–0.104 (–0.284 to 0.076)
MMD (+12 mm Hg)	None	–0.732 (–3.554 to 2.090)	0.931 (0.827 to 1.047)	–0.048 (–0.213 to 0.117)
	SBP	–1.440 (–4.286 to 1.406)	0.898 (0.817 to 0.986)	–0.096 (–0.261 to 0.069)
ARV (+2 mm Hg)	None	–1.518 (–2.302 to –0.734)	0.942 (0.864 to 1.026)	–0.004 (–0.137 to 0.129)
	SBP	–1.898 (–2.329 to –1.467)	0.918 (0.842 to 1.000)*	–0.036 (–0.165 to 0.093)

Abbreviations: SBP, systolic blood pressure; VIM, variability independent of the mean; MMD, the difference of maximum minus minimum systolic blood pressure; ARV, average real variability. Nighttime blood pressure (10 PM – 6AM) was obtained by 24-h ambulatory monitoring excluding the transition periods in the morning and evening when blood pressure rapidly changes. Model indicates which systolic index was entered into the models in addition to the predictor variable *per se*. None indicates that no other systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking and drinking. Significance of the estimates: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S6. Association of Organ Damage with Level and Variability of Morning Systolic Blood Pressure Self-measured at Home

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
SBP (+12 mm Hg)	None	0.876 (–2.064 to 3.816)	1.271 (1.130 to 1.430)‡	0.360 (0.195 to 0.525)‡
	VIM	0.924 (–2.016 to 3.864)	1.271 (1.130 to 1.430)‡	0.360 (0.195 to 0.525)‡
	MMD	0.840 (–2.100 to 3.780)	1.287 (1.143 to 1.448)‡	0.360 (0.195 to 0.525)‡
	ARV	0.888 (–2.052 to 3.828)	1.287 (1.143 to 1.448)‡	0.372 (0.207 to 0.537)‡
VIM (+2 units)	None	0.566 (–2.045 to 3.177)	0.963 (0.873 to 1.062)	0.010 (–0.139 to 0.159)
	SBP	0.624 (–1.998 to 3.246)	0.961 (0.875 to 1.055)	0.006 (–0.135 to 0.147)
MMD (+6 mm Hg)	None	0.858 (–2.000 to 3.716)	0.982 (0.883 to 1.092)	0.042 (–0.111 to 0.195)
	SBP	0.822 (–2.036 to 3.680)	0.953 (0.857 to 1.060)	0.0001 (–0.153 to 0.153)
ARV (+2 mm Hg)	None	1.064 (–1.382 to 3.510)	1.010 (0.927 to 1.101)	–0.032 (–0.161 to 0.097)
	SBP	1.068 (–1.386 to 3.522)	0.988 (0.910 to 1.073)	–0.064 (–0.189 to 0.061)

Abbreviations: SBP, systolic blood pressure; VIM, variability independent of the mean; MMD, the difference of maximum minus minimum systolic blood pressure; ARV, average real variability. Morning blood pressure was obtained by self-measurement at home. Model indicates which systolic index was entered into the models in addition to the predictor variable *per se*. None indicates that no other systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking and drinking. Significance of the estimates: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S7. Association of Organ Damage with Level and Variability of Evening Systolic Blood Pressure Self-measured at Home

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
SBP (+12 mm Hg)	None	1.380 (–1.301 to 4.061)	1.287 (1.171 to 1.413)‡	0.348 (0.207 to 0.489)‡
	VIM	1.320 (–1.385 to 4.025)	1.287 (1.171 to 1.413)‡	0.348 (0.207 to 0.489)‡
	MMD	1.512 (–1.216 to 4.240)	1.318 (1.200 to 1.448)‡	0.372 (0.207 to 0.537)‡
	ARV	1.392 (–1.313 to 4.097)	1.318 (1.200 to 1.448)‡	0.384 (0.219 to 0.549)‡
VIM (+3 units)	None	–0.744 (–3.619 to 2.131)	0.914 (0.822 to 1.016)	–0.042 (–0.201 to 0.117)
	SBP	–0.588 (–3.481 to 2.305)	0.900 (0.815 to 0.995)*	–0.063 (–0.216 to 0.090)
MMD (+9 mm Hg)	None	–0.720 (–3.807 to 2.367)	0.991 (0.891 to 1.102)	0.054 (–0.105 to 0.213)
	SBP	–0.990 (–4.112 to 2.132)	0.914 (0.822 to 1.016)	–0.063 (–0.222 to 0.096)
ARV (+4 mm Hg)	None	–0.160 (–3.492 to 3.172)	0.972 (0.871 to 1.085)	–0.032 (–0.204 to 0.140)
	SBP	–0.248 (–3.588 to 3.092)	0.901 (0.807 to 1.006)	–0.140 (–0.305 to 0.025)

Abbreviations: SBP, systolic blood pressure; VIM, variability independent of the mean; MMD, the difference of maximum minus minimum systolic blood pressure; ARV, average real variability. Evening blood pressure was obtained by self-measurement at home. Model indicates which systolic index was entered into the models in addition to the predictor variable *per se*. None indicates that no other systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking and drinking. Significance of the estimates: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S8. Association of Organ Damage with Classical Indexes of Blood Pressure Variability According to Recording Technique (Starts)

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
Beat-to-Beat Recording				
SBP (+ 13 mm Hg)	None	1.209 (–1.619 to 4.037)	1.169 (1.055 to 1.294)†	0.689 (0.562 to 0.816)‡
	SD	0.824 (–1.901 to 3.548)	1.147 (1.027 to 1.280)*	0.701 (0.560 to 0.841)‡
	CV	1.850 (–0.901 to 4.600)	1.164 (1.047 to 1.294)†	0.673 (0.537 to 0.808)‡
SD (+ 2.6 mm Hg)	None	4.176 (1.328 to 7.024)†	1.099 (0.988 to 1.221)	0.074 (–0.083 to 0.232)
	SBP	4.097 (1.229 to 6.965)†	1.060 (0.951 to 1.182)	–0.107 (–0.245 to 0.031)
CV (+ 1.8%)	None	3.579 (0.921 to 6.237)†	1.064 (0.957 to 1.183)	–0.085 (–0.242 to 0.072)
	SBP	3.885 (1.196 to 6.573)†	1.063 (0.958 to 1.231)	–0.091 (–0.224 to 0.043)
24-h Ambulatory Monitoring				
SBP (+ 12 mm Hg)	None	3.216 (0.605 to 5.827)*	1.241 (1.103 to 1.397)‡	0.420 (0.255 to 0.585)‡
	SD	3.107 (0.388 to 5.826)*	1.259 (1.128 to 1.405)‡	0.368 (0.208 to 0.528)‡
	CV	3.183 (0.559 to 5.807)*	1.220 (1.097 to 1.358)‡	0.433 (0.278 to 0.588)‡
SD (+ 3.1 mm Hg)	None	1.095 (–1.721 to 3.912)	0.986 (0.888 to 1.096)	0.252 (0.096 to 0.408)†
	SBP	0.120 (–2.777 to 3.018)	0.927 (0.834 to 1.031)	0.154 (–0.003 to 0.310)
CV (+ 2.4%)	None	–0.156 (–2.992 to 2.681)	0.914 (0.823 to 1.016)	0.102(–0.058 to 0.261)
	SBP	0.324 (–2.485 to 3.133)	0.937 (0.845 to 1.041)	0.159 (0.007 to 0.311)*

Table S8. Association of Organ Damage with Classical Indexes of Blood Pressure Variability According to Recording Technique (Continues)

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
Home Self-Measurement				
SBP (+ 11 mm Hg)	None	1.089 (–1.606 to 3.784)	1.274 (1.143 to 1.419)‡	0.363 (0.212 to 0.514)‡
	SD	1.027 (–1.843 to 3.897)	1.312 (1.179 to 1.461)‡	0.381 (0.220 to 0.541)‡
	CV	1.135 (–1.695 to 3.965)	1.292 (1.165 to 1.432)‡	0.372 (0.217 to 0.527)‡
SD (+ 2.2 mm Hg)	None	0.753 (–2.152 to 3.657)	1.004 (0.899 to 1.121)	0.066 (–0.098 to 0.230)
	SBP	0.571 (–2.384 to 3.525)	0.931 (0.834 to 1.039)	–0.040 (–0.204 to 0.123)
CV (+ 1.7%)	None	0.343 (–2.487 to 3.174)	0.949 (0.850 to 1.061)	–0.014 (–0.179 to 0.152)
	SBP	0.381 (–2.456 to 3.218)	0.935 (0.841 to 1.040)	–0.036 (–0.195 to 0.123)

Abbreviations: SBP, systolic blood pressure; SD, standard deviation; CV, coefficient of variation. Model indicates which systolic index was entered into the models in addition to the predictor variable *per se*. None indicates that no other systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the systolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking and drinking.
Significance of the estimates: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

Table S9. Association of Organ Damage with Indexes of Diastolic Blood Pressure Variability According to Recording Technique (Starts)

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
Beat-to-Beat Recording				
DBP (+ 8 mm Hg)	None	–0.003 (–2.749 to 2.743)	1.117 (0.997 to 1.254)	0.298 (0.132 to 0.464)‡
	VIM	0.263 (–2.489 to 3.014)	1.122 (1.000 to 1.257)*	0.302 (0.135 to 0.469)‡
	MMD	0.031 (–2.698 to 2.759)	1.113 (0.995 to 1.245)	0.295 (0.129 to 0.461)‡
	ARV	–0.049 (–2.788 to 2.689)	1.116 (0.995 to 1.251)	0.295 (0.128 to 0.461)‡
VIM (+ 1.8 units)	None	1.800 (–0.510 to 4.110)	1.051 (0.946 to 1.169)	0.050 (–0.106 to 0.207)
	DBP	1.828 (–0.510 to 4.165)	1.058 (0.952 to 1.176)	0.066 (–0.087 to 0.220)
MMD (+ 18 mmHg)	None	2.033 (–0.466 to 4.532)	1.179 (1.062 to 1.311)†	0.123 (–0.035 to 0.281)
	DBP	2.033 (–0.477 to 4.543)	1.177 (1.060 to 1.306)†	0.116 (–0.039 to 0.271)
ARV (+ 1 mmHg)	None	1.461 (–0.705 to 3.627)	1.040 (0.935 to 1.157)	0.086 (–0.072 to 0.244)
	DBP	1.462 (–0.715 to 3.638)	1.036 (0.931 to 1.153)	0.075 (–0.080 to 0.230)

Table S9. Association of Organ Damage with Classical Indexes of Blood Pressure Variability According to Recording Technique (Continues)

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
24-h Ambulatory Monitoring				
DBP (+ 10 mm Hg)	None	2.927 (–0.024 to 5.878)	1.229 (1.086 to 1.391)†	0.235 (0.049 to 0.422)*
	VIM	3.088 (0.092 to 6.085)*	1.224 (1.081 to 1.387)†	0.235 (0.047 to 0.424)*
	MMD	2.822 (–0.153 to 5.796)	1.228 (1.083 to 1.390)†	0.231 (0.043 to 0.419)*
	ARV	2.948 (–0.017 to 5.912)	1.226 (1.083 to 1.387)†	0.238 (0.052 to 0.425)*
VIM (+ 2.0 units)	None	0.506 (–2.411 to 3.423)	0.955 (0.858 to 1.064)	–0.029 (–0.191 to 0.132)
	DBP	0.986 (–1.931 to 3.902)	0.978 (0.879 to 1.088)	–0.001 (–0.162 to 0.160)
MMD (+ 9.6 mmHg)	None	1.374 (–1.798 to 4.545)	1.031 (0.921 to 1.154)	0.062 (–0.107 to 0.231)
	DBP	1.059 (–2.096 to 4.215)	1.013 (0.907 to 1.132)	0.042 (–0.126 to 0.211)
ARV (+ 1.3 mmHg)	None	0.384 (–2.617 to 3.385)	1.075 (0.964 to 1.198)	–0.077 (–0.240 to 0.085)
	DBP	0.506 (–2.462 to 3.473)	1.068 (0.961 to 1.189)	–0.084 (–0.245 to 0.077)

Table S9. Association of Organ Damage with Classical Indexes of Blood Pressure Variability According to Recording Technique (Continues)

Correlate (approximate SD)	Model	Left Ventricular Mass Index (g/m^2)	Albumin-to-Creatinine Ratio (mg/mmol)	Pulse Wave Velocity (m/s)
Home Self-Measurement				
DBP (+ 9 mm Hg)	None	0.445 (–2.573 to 3.463)	1.215 (1.076 to 1.373)†	0.180 (–0.005 to 0.364)
	VIM	0.530 (–2.524 to 3.584)	1.218 (1.078 to 1.376)†	0.180 (–0.004 to 0.365)
	MMD	0.461 (–2.573 to 3.495)	1.212 (1.073 to 1.369)†	0.179 (–0.006 to 0.364)
	ARV	0.441 (–2.593 to 3.476)	1.214 (1.075 to 1.372)†	0.182 (–0.003 to 0.366)
VIM (+ 1.4 units)	None	0.497 (–2.019 to 3.012)	1.040 (0.934 to 1.158)	0.012 (–0.149 to 0.173)
	DBP	0.553 (–1.993 to 3.099)	1.046 (0.941 to 1.163)	0.018 (–0.143 to 0.178)
MMD (+ 3.9 mmHg)	None	0.240 (–2.293 to 2.773)	1.064 (0.955 to 1.184)	0.027 (–0.134 to 0.188)
	DBP	0.259 (–2.287 to 2.805)	1.054 (0.948 to 1.172)	0.019 (–0.142 to 0.179)
ARV (+ 1.5 mmHg)	None	–0.097 (–2.868 to 2.675)	1.035 (0.928 to 1.155)	–0.035 (–0.199 to 0.128)
	DBP	–0.078 (–2.863 to 2.708)	1.028 (0.923 to 1.145)	–0.042 (–0.205 to 0.121)

Abbreviations: DBP, diastolic blood pressure; SD, standard deviation; CV, coefficient of variation. Model indicates which diastolic index was entered into the models in addition to the predictor variable *per se*. None indicates that no other systolic index was entered in addition to the studied predictor variable. Effect sizes (95% confidence interval) express the change in the target organ damages with a 1-SD increase in the diastolic predictors. All models were adjusted for sex, age, body mass index, heart rate, plasma glucose, serum cholesterol, smoking and drinking.
Significance of the estimates: * $P \leq 0.05$; † $P \leq 0.01$; and ‡ $P \leq 0.001$.

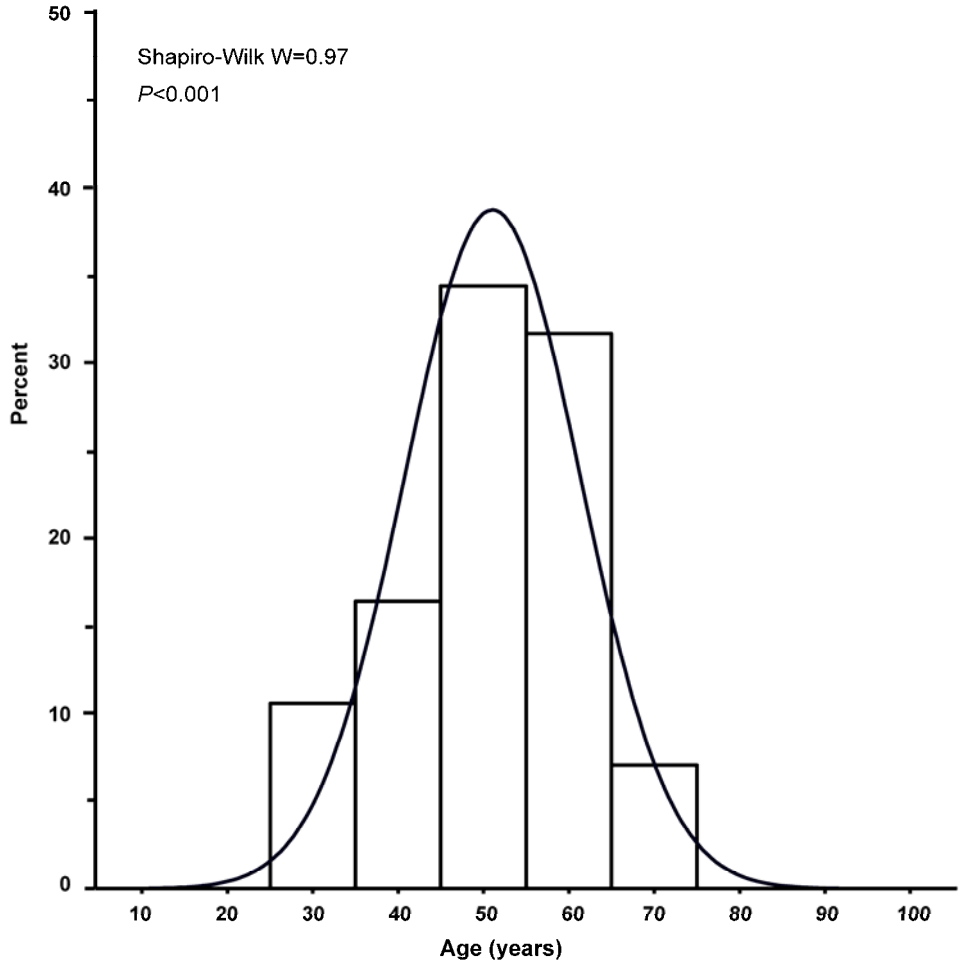

Figure S1. Frequency distributions of age in the 256 study participants. Shapiro-Wilk W static for normal test is presented. The *P* value is for departure of the actually observed distribution (solid line) from normality.